Chapter 10
Natural History and Long-Term Clinical Outcome After Conservative and Surgical Management

Won-Sang Cho and Jeong Eun Kim

Abstract  Moyamoya disease (MMD) is a rare but interesting subject in the field of cerebrovascular diseases because of its unique angiographic features and clinical characteristics, partly satisfactory surgical outcomes, and still unknown cause and remaining controversies. Here, the authors reviewed the previous studies about both pediatric and adult MMD with our experience in the management of adult patients. Taking a look at the natural history of MMD, the significance of surgical treatment for ischemic and hemorrhagic presentation was considered. Bypass surgery seems to be effective in prevention of ischemic stroke; however, the perioperative complications are the big obstacle to change the natural clinical course. Among surgical skills, combined bypass surgery is expected to have a better role than indirect surgery in the long term, in terms of the extent of flow augmentation and detailed neurological/cognitive functions. Until now, however, gross clinical outcomes look not so different between combined and indirect procedures. The effectiveness of surgery to prevent from rebleeding in hemorrhage MMD is still inconclusive. Antiplatelet medication may be effective in some situations with no increase in hemorrhagic complication. Now, randomized prospective study is needed to make a standard treatment guideline, and basic research should be kept parallel to clinical studies to find out the causes, stop the progression, and apply the appropriate treatment modalities.

Keywords Moyamoya disease • Natural history • Bypass surgery • Outcome • Complications
10.1 Natural History of Moyamoya Disease (MMD)

10.1.1 Ischemic MMD

There have been few studies about the natural history of pure pediatric MMD [11, 19], but most of studies have dealt with mainly adult MMD with a small number of pediatric patients [6, 7, 13, 14, 20, 36, 38, 44, 56]. Choi et al. reported that 33.3% of adult and 60% of pediatric patients were aggravated in ischemic symptoms during conservative management [11]. Imaizumi et al. reported that 60% of nonsurgical patients ranged from disabled to death during follow-up [19]. Patients younger than 3–5 years tended to show rapid progression and poor surgical outcomes [32]. Although recuperative power is greater in pediatrics than adults, development delay, cognitive dysfunction, and chronic seizure as well as neurological deficits can occur in the developing brain. In such reasons, most of symptomatic pediatric patients have undergone bypass surgery, and the results are satisfactory [11, 19, 31, 40, 48].

Reviewing severe studies about the natural clinical course of adult MMD [6, 7, 13, 14, 36, 44, 55], recurrence rate of stroke such as infarction and hemorrhage is quite considerable than expected although there is some difference among ethnic groups. Here we are to think about the ischemic MMD, dealing with the hemorrhagic MMD in the latter part. According to the Hallemeier et al.’s study following 34 adult patients over 5.1 years [14], 5-year stroke occurrence was about 65%. Gross et al. reported that infarction and hemorrhage respectively occurred in 13.3%/person-year and 1.7%/person-year during 2.9-year follow-up of 42 adult patients [13]. In Chiu et al.’s study [6], 35 patients experienced 10.3%/person-year of stroke during 40 months, which consisted of 1.7% of hemorrhage and 8.6% of ischemic symptoms. In our natural course study following 241 adult MMD patients with hemodynamic stability (more than 50% of reserve capacity) and mild symptoms [7], overall stroke rate was 4.5%/person-year in which hemorrhage and ischemia were 2.3% and 2.2%, respectively. Clinical outcome was worst in patients with hemorrhagic presentation other than ischemic and asymptomatic presentations. Initial clinical presentation tended to recur, and patients with family history of MMD showed high occurrence of stroke. Noh et al.’s recent study showed that 1- and 5-year recurrence rates in patients with ischemic MMD under conservative management were 1.6% and 11.8%, respectively [46]. Risk factors of recurrent ischemic stroke included hypertension, diabetes mellitus, decrease in reserve capacity, and stenosis at the posterior cerebral arteries.

Asymptomatic MMD patients are considered to have not a low incidence of stroke [7, 20, 38, 56]. In our recent study [7], 35 adult patients with asymptomatic MMD showed 2.5%/person-year of hemorrhage and 0.8% of ischemic stroke. Five-year stroke rate was about 15%, and asymptomatic patients showed best clinical course, compared to the patients with hemorrhagic or ischemic presentations. Kuroda et al. analyzed that 40 patients presented with 3.2%/person-year of stroke for a mean follow-up of 43.7 months, in which hemorrhage and infarction each were 2.4% and 0.8% [38]. Twenty-one percent of the patients eventually experienced
neurological symptoms; however, 97.5% of them showed tolerable neurological status (modified Rankin score of 2 or less). Yang et al. showed 4% of hemorrhage and 1.3% of ischemia in 42 patients with 75 hemispheres during the mean 37.3 months [56]. Risk factor of clinical deterioration was solely the preoperative decrease in cerebrovascular reserve capacity. Jo et al.’s report showed 7.5% of transient ischemic attack and none with infarction and hemorrhage in 40 adults with 74 hemispheres for about 32 months [20]. Risk factors included smoking and compromise in preoperative reserve capacity. Therefore, routine follow-up should be performed in patients with asymptomatic presentation, especially in those with risk factors.

10.1.2 Hemorrhagic MMD

Majority of pediatric patients present with ischemic symptoms, and about 3% of them is known to manifest cerebral hemorrhage [3]. Meanwhile, adults present with cerebral hemorrhage in about 20–30% [7]. Generally, intraventricular hemorrhage is more common than intracerebral hemorrhage [30], and bleeding risk factors include cerebral microbleeds, older age, presence of prominent anterior choroidal, and posterior communicating arteries [24, 36, 43–45, 52].

It is well known that hemorrhagic MMD usually has a poor clinical course if untreated [7, 36, 42, 44]. According to Kobayashi et al.’s study, 33.3% of the patients experienced rebleeding for a mean follow-up of 80.6 months, recovery rate after rebleeding decreased into half of that after initial bleeding, and mortality rate increased four times [36]. Morioka et al. reported that rebleeding occurred in 61.1% of the patients during 12.7 years, and 77.3% of the patients with rebleeding were clinically aggravated [44]. Presenting age of the initial bleeding 36 years or more was a risk factor of rebleeding. In a recent prospective study from Japan [42], rebleeding rate was 34.2% in patients untreated for 5 years. As the follow-up period was longer and patients were older, rebleeding rate was considered to increase. A risk factor of rebleeding in the same patient group was analyzed as the initial posterior hemorrhage which was defined as one attributable to perforating arteries from the posterior cerebral artery or choroidal arteries, including those located in the thalamus, posterior half of the temporal lobe, parietal lobe, occipital lobe, subependymal area of the posterior part of the lateral ventricle including the trigon, or posterior half of the corpus callosum [53].

10.1.3 Fate of Unilateral MMD

Previously, unilateral involvement with moyamoya vessels and unknown causes was defined as probable MMD. As the cases of unilateral involvement increase and bilateral progression is well known [16, 18, 21, 25, 27, 28, 39, 41, 47, 57], however, unilateral involvement in children became definitive MMD in the 2012 Japan
Incidence of unilateral MMD is about 8.5–20%, 0–58.8% of which is reported to progress into the bilateral disease [16, 18, 25, 39, 41, 47, 57]. The reason why the incidences of bilateral progression are widely various is thought to be related with the various range of follow-up duration from 13 to 73 months and the different ethnicity. Prognostic factors of bilateral progression included vascular abnormality contralateral to the involved side of internal carotid artery, female, younger age, and family history [25, 39, 41, 47, 57]. Progression of bilateral involvement as well as disease stage is known to be more rapid and commonly occur in pediatrics than in adults. However, progression in adult patients is recently thought as frequent as in pediatrics [39, 41]. Therefore, patients with unilateral involvement should be managed based on the clinical symptoms and diagnostic results. Moreover, routine imaging follow-up is needed (Fig. 10.1).

### 10.2 Surgical Outcomes

#### 10.2.1 Ischemic MMD

Surgical outcomes in ischemic MMD are satisfactory. Most of pediatric cases were treated with indirect bypass surgery, with a stroke risk of 0.2–1.6%/year after surgery [31]. In addition, most of them surgically treated grew up well and had a normal life [48]. On the other hand, there has been a mood of superiority of direct/combined bypass surgery over indirect procedure in adult patients even though there is no high level of evidences. The stroke risk is known to be 0–1.6%/year after direct/combined bypass surgery and 0–14.3%/year after indirect bypass [34].
10.2.1.1 Surgery vs Conservative Management

Few comparative studies about the conservation and surgery exist. Choi et al.’s observation study about pediatric MMD said that 57% of the patients with conservative management became aggravated; however, 14% of those who got surgery became worse [11]. According to a recent meta-analysis comparing surgery to conservative management in all aged patients with MMD [49], stroke risk was significantly lower in surgery group than conservative group. In our long-term surgical outcome in terms of clinical, angiographic, and hemodynamic aspects [8], all the aspects continued to improve till 6 months after surgery and thereafter became stationary in 5 years. Five-year infarction- and hemorrhage-free survival rates were 98.7% each, and infarction and hemorrhagic risks were 0.2% and 0.4%/person-year, respectively (Fig. 10.2). Considering the natural history of hemodynamically stable MMD patients in our institution as 2.2%/person-year of infarction and 2.3% of hemorrhage (Fig. 10.3) [7], stroke recurrence rate is much lower in surgery group than in observation group although the surgery group had worse preoperative conditions than observation group. Merely, permanent postoperative complication rate was 3.9%, for which a few years would be needed to overcome the natural history of conservative group. Recently, our affiliated group retrospectively compared direct/combined bypass surgery group of 301 adults in their institution to observation group of 140 patients in our institution [35]. One- and 5-year ischemic stroke rates did not differ; however, 10-year rate was superior in surgery group than observation group (3.9% versus 13.3%). In addition, the only independent protective factor was bypass surgery. Postoperative stroke complication rate in this study was
2.7%, and more than 5 years of time period was needed for surgical benefit to overcome the natural history of observation group (Fig. 10.4). So, complication rate of each institution’s own as well as patients’ condition and age should be considered before deciding the surgery.

10.2.1.2 Direct/Combined vs Indirect Bypass Surgery

According to some comparative studies between direct/combined and indirect bypass surgeries in adult MMD [1, 4, 8, 26], overall neurological outcomes are similarly satisfactory; however, detailed clinical outcomes were better, and angiographic areas were wider in direct/combined bypass than indirect procedures. A recent meta-analysis showed that long-term prevention of hemorrhage and ischemia and favorable clinical outcomes were better in direct/combined procedures, although overall complication rates were not different [51]. Kazumata et al.’s systemic review analyzed that there was no difference in postoperative stroke complication between direct/combined and indirect surgeries (7.6% versus 5.1%, respectively); however, neorevascularization was significantly better in direct/combined procedures [23]. Moreover, comparing some patients with long-term follow-up of about 4 years, recurrent stroke rate was higher in indirect bypass surgery (11.2% versus 3.5%). We once analyzed the short-term outcomes of combined and indirect bypasses although unpublished, in which clinical and hemodynamic outcomes were similar; however,
Fig. 10.4  Survival curves of any stroke (a), ischemic stroke (b), and hemorrhagic stroke (c). A steep slope shortly after 0 month means perioperative stroke events. In around 5 and 7 years after surgery, natural course in surgery group becomes better than that in observation group (Modified from Kim et al. [36] under the permission by American Association of Neurological Surgery)
revascularization area was significantly wider in combined bypass group. Which clinical impact would be had on by wider revascularization after combined bypass surgery is needed to be observed for a longer period. As most of cases reported on papers are small numbers and different in basal characteristics, evaluation modalities, surgical skills, and follow-up period, which kind of bypass surgery be more advantageous is still hard to determine. Merely, considerable exercise and experience are needed to perform direct bypass surgery. Thus, if direct bypass is not available, indirect bypass surgery can be a good alternative.

10.2.2 Hemorrhagic MMD

Bypass surgery for ischemic MMD is well known to be effective in both pediatric and adult patients [34]. Meanwhile, the efficacy of bypass surgery in preventing from rebleeding in hemorrhagic MMD has been controversial. A 10-year prospective study concluded that there was no significant difference in rebleeding risk between surgery and non-surgery groups [55]. A recent meta-analysis showed the protective effect of bypass surgery on the rebleeding [49]. According to a multicenter prospective and randomized trial from Japan [42], surgery group showed significantly lower incidence of rebleeding than non-surgery group (14.3% versus 34.2%). Annual rebleeding rate was 3.2%/year in surgery group and 8.2%/year on conservative group. This trial is the only prospective and randomized study, and there was no dropout case during follow-up. However, the result is not considered to be complete because the statistical significance varied according to the statistical methods. So, further study is needed.

10.2.3 Cerebral Hyperperfusion Syndrome (CHS) and Other Complications

Postoperative complications include infarction, hemorrhage, cerebral hyperperfusion syndrome, wound problem, infection, and so on. Complication rate is reported in about 1.6–16%, among which permanent ischemic complication is 0.9–8% and permanent hemorrhagic one is 0.7–8%, and the occurrence is more common in adult patients [23, 34]. Noh et al. reported that 50% of ischemic stroke occurred within 1 month after surgery and 1- and 5-year stroke recurrence rates were 24.4% each [46]. In our long-term surgical outcomes [8], 5-year infarction and hemorrhage risks were 1.3% each; however, permanent perioperative neurological complication rate was 6.7%. Therefore, perioperative management to prevent or recover from complications is a critical step to improve the surgical outcomes.

CHS is well documented in patients with carotid stenosis, and it was also identified in adult patients with MMD after low-flow direct bypass surgery [12, 29].
In our previous report, the incidence of clinical CHS was identified in 17% of the patients, and cerebral hyperperfusion became maximal around in the third day after surgery [29]. The presumptive pathomechanism is transient dysfunction of cerebral autoregulation: autoregulatory function has been chronically impaired, and clinical symptoms corresponding to the hyperperfusion areas by direct bypass pedicle can occur until the recovery of its function. CHS is reported to occur in about 21.5–50% after direct bypass surgery [34], and various clinical symptoms manifest from headache to neurological deficits and intracerebral hemorrhage. We experienced similar situations even after indirect bypass surgery for adult MMD [10]. Hyperperfusion corresponding to the clinical symptoms was identified on brain single-photon emission computed tomography. It is not clear whether this was real hyperperfusion or manifestation by different mechanisms; however, similar suspicion was also identified in pediatric cases after indirect bypass surgery. So, we plan to keep a close watch about it. When CHS is suspicious after combined bypass surgery in our institution, brain computed tomography + diffusion-weighted magnetic resonance (MR) imaging or MR imaging with diffusion-weighted images + susceptibility-weighted images + arterial spin labelling images are acquired to differentially diagnose hemorrhage, infarction, and CHS. After CHS is diagnosed, protocolized medical management is started: normotension or slight hypotension within −10% of the usual systolic blood pressure, normohydration, and the transient use of steroid.

### 10.2.4 Other Surgical Considerations

#### 10.2.4.1 Coverage of Other Territories Beyond the Middle Cerebral Artery (MCA) Territory by Bypass Surgery at the Cortical Branches of MCA

There are many kinds of surgical skills for MMD which are as follows: direct/combined bypass and indirect bypass; single- and double-barrel direct bypass; encephaloduroarterio-, encephalgaleo-, and encephalomyo-synangiosis as indirect bypass; and multiple burr hole trephination. Irrespective of the surgical skills, most of them are performed at the MCA territory because MCA territory is the widest, most of clinical symptoms are related with MCA, surgery at the MCA territory is feasible, and surgical outcomes have been satisfactory. Rarely, bypass surgery at the other territories, such as anterior (ACA) and posterior cerebral arteries (PCA), has been reported on occasion [15, 22]. Except for some cases necessitating other kinds of bypass surgery, our institution has generally performed superficial temporal artery-MCA single pedicle microanastomosis and encephalodurogaleosynangiosis, resulting in satisfactory outcomes [8]. Recently, we found out that combined bypass surgery at the MCA territory could improve the ACA as well as MCA-related hemodynamic and clinical states (Fig. 10.5) [9]. Such phenomenon was more prominent in patients with preoperative symptoms related to ACA territory. According to a systemic review [23] and our unpublished data, revascularization area seems to be
wider in combined bypass surgery than in indirect procedure. Although previous studies failed to show a significant difference in clinical outcomes between combined/direct and indirect bypass surgeries [1, 4, 8, 23, 26, 51], combined bypass surgery is thought to be more beneficial in cases necessitating wider flow augmentation, for example, accompanying ACA or PCA as well as MCA-related symptoms, and considering the cognition as an important function of medial frontal lobe. In the same vein, double-barrel direct bypass surgery with indirect procedures may be more effective than single direct bypass in patients with hemodynamic impairment beyond the MCA territory. Kim et al. compared two different surgical skills (indirect bypass at MCA territory alone versus indirect bypass at MCA and ACA territories) in pediatric patients [33]. Additional indirect bypass at the ACA territory significantly improved ACA-related symptoms and surgical outcomes in terms of hemodynamic and angiographic states. Considering case-by-case conditions, personalized surgical strategies would be more helpful.

Fig. 10.5 A case of 35-year adult MMD patient treated with right-sided combined bypass surgery (superficial temporal artery angular branch of middle cerebral artery single direct bypass + encephalogaleosynangiosis). Preoperative evaluation exhibited near occlusion of right distal ICA with limited basal moyamoya vessels on cerebral angiography (a), decrease in basal perfusion (b) and reserve capacity (c) of right ICA territory on Diamox® single-photon emission computed tomography, and subacute infarction at the right corona radiata on MR imaging (d). On 6-month follow-up work-up, abundant revascularization dominantly by direct pedicle in the territories of ACA as well as MCA (e and f) was demonstrated with a finding of regression of the right distal ICA and basal moyamoya vessels (e). In addition, basal perfusion (g) and reserve capacity (h) much improved.
10.2.4.2 Role of Direct and Indirect Bypasses in the Combined Surgery

The roles of indirect flap and direct pedicle in the combined bypass surgery have long been discussed. One opinion is that direct pedicle would play a dominant role for flow augmentation, and the other is that indirect flap would become dominant and direct pedicle slowly regress [8, 17, 54]. In our previous study [8], revascularization area continued to widen until 5 years after surgery, while dominant, complementary, and poor developments of direct or indirect components were various and the patterns changed over time. One of the interesting findings was that the incidence of occlusion of direct pedicle was 6.6% in 6 months after surgery and 23% in 5 years. So, it was speculated that direct pedicle would play a role of acute flow augmentation in the early phase and indirect flap would replace the areas in which blood flow from direct pedicle could not reach because of the progressive occlusion of the intracranial arteries (named compartmentation) in the later phase. This hypothesis is indirectly confirmed also in Uchino et al.’s recent report [54], in which dominancy of indirect and direct bypass differed in pediatric and adult patients; however, each component of indirect and direct bypass showed reciprocal roles, and development of indirect bypass was significant in patients with advanced stages of MMD (Suzuki grade 4 or more). Therefore, direct and indirect bypasses seem to play complementary roles according to the temporal and spatial situations. In that sense, combined bypass surgery may be superior to direct or indirect procedures alone.

10.3 Medical Management

Angiographic feature of MMD is the progressive steno-occlusion of the distal internal carotid artery and proximal anterior and middle cerebral arteries. Histologic feature is the intimal thickening by proliferation of smooth muscle cells with no inflammatory/atheromatous changes. The cause of MMD is still idiopathic, and it is different from the intracranial atherosclerotic stenosis or vasculitis accompanying endothelial damage. So, there have been no fundamental treatment modalities; instead, symptomatic medical treatment and bypass surgery for flow augmentation have been performed. Among the medical treatment, the use of antiplatelets has been controversial. Because the main pathophysiology in MMD is the hemodynamic insufficiency following steno-occlusion of the intracranial vessels, drugs, such as antiplatelets inhibiting platelet adhesion/aggregation and statin stabilizing the plaque, are traditionally considered not effective. However, microthromboembolism is reported to occur even in MMD, and it was closely related with the development of ischemic events [5]. In addition, atherosclerotic vessel change can be superimposed as adult patients get older, and drugs can be selectively needed in order to maintain the patency at the bypass site. According to a recent Kraemer et al.’s report, about 31% of the responders used antiplatelets for the MMD patients [37]. Interestingly, Asian experts tended to prescribe antiplatelets less frequently.
than Western doctors, the reason of which was speculated that Asian patients show higher incidence of hemorrhagic presentation. Actually, there is ethnic difference in hemorrhagic presentation: less than 15% in Western countries, 29% in Hawaii where the proportion of Asian inhabitants is high, and 30–60% in East Asian countries [2, 7]. A recent prospective study reported that ischemic events did not differ between antiplatelet and non-antiplatelet groups, and hemorrhagic events were higher in the non-antiplatelet group than in the antiplatelet group [55]. Further studies are needed to make a conclusion in the use of antiplatelets.

References